

REMARKS

Applicants respectfully request entry of the present amendments to the claims and consideration of the following remarks. All prior rejections and objections are respectfully traversed.

STATUS OF CLAIMS

Claims 1-3 and 6-15 are pending. Claims 1, 3, 8, and 15 are amended. Claims 19 and 20 are new. Claim 1 has been amended to include the term "about" before the numerical values relating to pH, and in other minor respects. Support for these amendments may be found throughout the specification, for example, at page 9, lines 15-17. Claim 1 has been further amended to include the "polyol" limitation of claim 3, and to specify that the "aqueous" material is in a "liquid" form. This amendment is supported throughout the specification, for example, at page 3, lines 27-28. Claim 8 is amended to correct claim dependency. Claim 15 is amended to correct a typographical error. New claim 19 finds support throughout the specification, for example, at page 9, lines 15-17 and in original claim 1. No new matter has been added by any of the amendments submitted herein.

REJECTION UNDER § 102(B)

Claims 1, 3, 6, 7, 12, and 13 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by US 6,432,449 (Goldenberg). This rejection is not well taken and should not be maintained.

The present disclosure relates to stable pharmaceutical compositions of a protein, namely, granulocyte-colony stimulating factor (G-CSF). The G-CSF of the present case may be expressed heterologously in the bacteria *E. coli* and, as such, is generally provided in a non-glycosylated form. G-CSF, and especially non-glycosylated G-CSF, is known to be a relatively hydrophobic protein, typically substantially insoluble in aqueous systems under biological conditions. Non-glycosylated G-CSF is also known to be relatively unstable in preparations *in vitro*, having a tendency to produce aggregations of limited bioavailability, so various additives such as surfactants have been proposed with respect to conventional preparations in order to increase the

stability and solubility of the protein. These additives may be undesirable for use in pharmaceutical preparations, however, as described in page 3, fifth full paragraph of the specification. The present invention provides, among other things, a method of making aqueous liquid pharmaceutical preparations of biologically active, recombinant, non-glycosylated G-CSF having a relatively long shelf life, without the need for surfactants.

Independent claim 1 defines, inter alia, a stable aqueous liquid pharmaceutical composition of G-CSF having a pH in the range from about 4.2 to about 4.8 and comprising a therapeutically effective amount of non-glycosylated G-CSF, a polyol, and an acid, wherein the composition is substantially free of any surfactant. Applicants have found that the claimed composition is surprisingly stable and bioavailable in liquid form, has a relatively long shelf life, is physiologically well-tolerated, is simple to use, and is amenable to be dosed precisely. (See page 3, lines 27-32).

Goldenberg

Goldenberg is said to disclose a sustained release formulation containing biodegradable alginate delayed gels or particles and methods thereof. Example 5 was said to anticipate Applicants' claims. However, the gel of Example 5 does not anticipate claim 1 for at least the reason that it does not contain a polyol, and it is not a stable aqueous liquid pharmaceutical composition.

The previous Office Action asserted that the ethyl ester alginate of Goldenberg is only one third esterified and according to the definition of the polyol in the instant specification, such a material would be considered a polyol as claimed. With all due respect, this is in error. The present specification defines a polyol as any polyhydric alcohol. Partially esterified ethyl ester alginate is not a polyhydric alcohol as called for in the claims. One of ordinary skill in the art would not regard a partially esterified alginate as a polyol or a polyhydric alcohol, since it is not an alcohol containing two or more hydroxyl groups. Therefore, Example 5 of Goldenberg plainly would not disclose

a "polyol" called for in claim 1 to a person of ordinary skill.¹

Claim 1 also calls for an aqueous liquid pharmaceutical composition. Nothing in Goldenberg discloses or teaches such a composition. Goldenberg teaches the formation of gels. While the materials in Goldenberg might be liquid at some point during their manufacture, they are not disclosed or taught to be stable in aqueous liquid form. The liquid state is only temporary, being described in Goldenberg as "liquid mixtures for time delay gelation." (See for example, column 3, lines 51-56; column 4, lines 13-15; column 10, lines 43-50; column 10, lines 55-61; and Example 5). The pre-gelled state of the Goldenberg compositions is a transitory, unstable intermediate stage in the process, and not a stable pharmaceutical composition as claimed.

Therefore, claim 1 and dependent claims 3, 6-7, 12, and 13 are not anticipated by Goldenberg. Further, new claim 19, being dependent from claim 1, is likewise novel over Goldenberg. Accordingly, allowance of claims 1, 3, 6-7, 12, and 13 is hereby respectfully requested.

REJECTIONS UNDER § 103(A)

Claims 1-3, 6-9, and 12-15 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over US 6,875,432 (Liu) in view of US 5,284,656 (Platz) and in further view of US 6,776,983 (Sumida). As will be shown, this rejection was also not well taken and should not be maintained.

Independent claim 1 defines, inter alia, a stable pharmaceutical aqueous liquid composition of granulocyte-colony stimulating factor (G-CSF), wherein the composition has a pH in the range from about 4.2 to about 4.8 and comprises a therapeutically effective amount of non-glycosylated G-CSF, a polyol, and an acid, wherein the composition is substantially free of any surfactant. The claimed composition is shown to exhibit a relatively long shelf life, to be physiologically well-tolerated, to be simple to use, and to be dosible more precisely. (See page 3, lines 27-32).

¹ The definition of polyhydric alcohol is rectified by the above specification amendment. Any person of ordinary skill would know a polyhydric alcohol is an alcohol having two or more hydroxyl groups. See attached copy of Hawley's Condensed Chemical Dictionary, Eleventh Edition at p. 940.

G-CSF pharmaceutical formulations have conventionally contained surfactants to prevent aggregation and denaturation at packing material surfaces. Applicants have found a way to provide stable pharmaceutical G-CSF aqueous liquid compositions which exhibit relatively good bioavailability and other properties without the need for surfactants. One of skill in the art would be taught by Liu, Platz, and/or Sumida to include a surfactant in their respective compositions according to what has been conventional in the art. Nothing in any of these references (or any combination of them) would direct a person of skill even attempt a surfactant-free pharmaceutical G-CSF composition in aqueous liquid form.

Liu discloses a concentrated protein formulation with what is said to be a reduced viscosity suitable for subcutaneous administration. (See Abstract). Liu describes the conventional and expected surfactant component in its protein formulations (see column 25, lines 18-40). Specific surfactants are taught in at least Examples 1-4. Therefore, one of skill in the art reading Liu would be led to use a surfactant in a final proteinaceous formulation according to conventional practice.

Platz describes compositions of G-CSF said to be suitable for aerosol administration through the lungs. Platz teaches what is said to be "an effective non-invasive" pulmonary administration of G-CSF. (See column 2, lines 60-62). Surfactants are repeatedly specified throughout Platz, for example, see column 3, line 62 through column 4, line 3; column 4, lines 6-17; and column 7, lines 16-22. Further, surfactants were said to have been used in all the examples. (See Table 2 and column 8, line 66 through column 9, line 31). (Note that this is the case even though surfactants were said not to be necessary in "aerosol" formulations, see Column 8, lines 1-14).

While one of skill in the art reading Liu would have no reason to seek the guidance of Platz (the two references are directed to two entirely different drug delivery formulations), one who happened to read both references would still be taught to include a surfactant according to what was thought to be conventional in the art at the time. Any person of ordinary skill in the art would see nothing in Liu and Platz to

change the standard approach of including a surfactant in any aqueous liquid G-CSF formulation.

Sumida discloses a G-CSF formulation comprising at least one pharmaceutically acceptable surfactant. The formulation is also taught to have a pH in the range of 6-6.8 (see claim 1). Of some importance is the fact that the Sumida formulation is said to be substantially free of any protein “stabilizer.”

One of ordinary skill in the art reading Liu would not be motivated to attempt to fashion any combination with Sumida. Sumida discloses a formulation that is specifically said to be free of any protein “stabilizers.” Liu, on the other hand, discloses Zn-protein complexes as suitable stabilizers. (See column 25, lines 52-58). There is no way to even consider combining the two references except by a route of impermissible hindsight after reading the present application and ignoring the explicit incompatibility of the references vis-à-vis the discordant inclusion / exclusion of so-called protein “stabilizers.” These documents stand as unrelated and seemingly incompatible references with no apparent commonality vis-à-vis Applicants’ claimed invention.

Even if one did by some happenstance consider all three of these references together, the fact remains that Liu, Platz, and Sumida explicitly disclose the apparent necessity of a surfactant as a component of any mixture. Therefore, one attempting to read these references together (and there is no reason they would ever do so), would very plainly be taught to include a surfactant in any resulting formulation according to standard operating procedure. This is not claim 1, which requires the composition to be, among other things, an aqueous liquid free of any surfactant.

Therefore, independent claim 1 and its dependent claims 2-3 and 6-15 patentably distinguish over Liu, Platz, and Sumida. Reconsideration and allowance of claims 1-3 and 6-15 are hereby respectfully requested. For at least these reasons, new claim 19 is likewise nonobvious over the cited references.

Nonstatutory Obviousness-type Double Patenting Rejection

Claims 1-3 and 8-11 are “provisionally” rejected over claims 1-10 of copending Application No. 10583157. Copending Application No. 10583157 claims a priority date of December 23, 2003. The present application claims a priority date of November 4, 2003. Accordingly, the Examiner’s perceived double patenting issue would appear to be reversed. Since copending Application No. 10583157 has not yet been substantively examined and it is the later-filed application, Applicants submit that should the conditions still warrant, a nonstatutory obviousness-type double patenting rejection (and the possible need for a Terminal Disclaimer) might be proper in copending Application No. 10583157, but not in the present application.

Should Applicants be incorrect in their understanding and should the nonstatutory obviousness double patenting rejection be the only remaining rejection, Applicants would then submit a proper terminal disclaimer in accordance with 37 CFR 1.321(c) to remove the rejection, upon allowance of claims in a prior-filed co-pending application. Accordingly, reconsideration and allowance of claims 1-3 and 8-11 are hereby respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

FEES

The Applicants do not believe that there are any fees associated with this filing. However, if the calculations are incorrect, the Commissioner is hereby authorized to charge any deficiencies in fees or credit any overpayment associated with this communication to Deposit Account No. 12-2355. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 12-2355.

Respectfully submitted,

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Hawley's Condensed Chemical Dictionary

ELEVENTH EDITION

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polymer, stereospecific. (stereoregular).

A polymer whose molecular structure has a definite spatial arrangement, i.e., a fixed position in geometrical space for the constituent atoms and atomic groups comprising the molecular chain, rather than the random and varying arrangement that characterizes an amorphous polymer. Achievement of this specific steric (three-dimensional) structure (also called tacticity) requires use of special catalysts such as those developed by Ziegler and Natta about 1950. Such polymers are wholly or partially crystalline. Synthetic natural rubber, *cis*-polyisoprene, is an example of a stereospecific polymer made possible by this means. There are five types of stereospecific (or stereoregular) structures: *cis*, *trans*, isotactic, syndiotactic, and tritactic.

See also catalyst, stereospecific.

polymer, syndiotactic. See syndiotactic polymer.

polymer, synthetic. See polymer.

polymer, water-soluble. Any substance of high molecular weight that swells or dissolves in water at normal temperature. These fall into several groups, including natural, semisynthetic, and synthetic products. Their common property of water solubility makes them valuable for a wide variety of applications as thickeners, adhesives, coatings, food additives, textile sizing, etc.

See specific entries.

(1) *Natural*. This type is principally comprised of gums, which are complex carbohydrates of the sugar group. They occur as exudations of hardened sap on the bark of various tropical species of trees. All are strongly hydrophilic. Examples are arabic, tragacanth, karaya.

(2) *Semisynthetic*. This group (sometimes called water-soluble resins) includes such chemically treated natural polymers as carboxymethylcellulose, methylcellulose, and other cellulose ethers, as well as various kinds of modified starches (ethers and acetates).

(3) *Synthetic*. The principal members of this class are polyvinyl alcohol, ethylene oxide polymers, polyvinyl pyrrolidone, polyethyleneimine.

polymethacrylate resin. See acrylic resin, methyl methacrylate.

polymethylbenzene. See durene and pseudocumene, the two members of this group with some commercial production and use.

polymethylene polyphenylisocyanate.

A polymer of diphenylmethane-4,4' diisocyanate.

polymethylene wax. See wax, polymethylene.

poly-4-methylpentene-1.

Properties: High resistance to all chemicals except carbon tetrachloride and cyclohexane, excellent heat resistance, high clarity and light transmittance. Temperature limit 170°C, *d* 0.83.

Use: Laboratory ware (beakers, graduates, etc.), electronic and hospital equipment; food packaging, especially types subject to high temperature such as trays for TV dinners, etc.; light reflectors.

poly(methyl vinyl ether). See polyvinyl methyl ether.

polymorphism. See allotropy.

polymyxin. CAS: 1406-11-7. Generic term for a series of antibiotic substances produced by strains of *Bacillus polymyxa*. Various polymyxins are differentiated by the letters A, B, C, D, and E. All are active against certain gram-negative bacteria. Polymyxin B is most used.

Properties: All are basic polypeptides, soluble in water; the hydrochlorides are soluble in water and methanol, insoluble in ether, acetone, chlorinated solvents, and hydrocarbons. Permissible food additives.

Use: Medicine (antibiotic), beer production.

polynuclear. Descriptive of an aromatic compound containing three or more closed rings, usually of the benzenoid type, e.g., sterols. See also polycyclic, nucleus (3).

polyol. A polyhydric alcohol, i.e., one containing three or more hydroxyl groups. Those having three hydroxyl groups (trihydric) are glycerols, those with more than three are called sugar alcohols, with general formula $\text{CH}_2\text{OH}(\text{CHOH})_n\text{CH}_2\text{OH}$, where *n* may be from 2 to 5. These react with aldehydes and ketones to form acetals and ketals.

See also alcohol, glycerol.

polyolefin. A class or group name for thermoplastic polymers derived from simple olefins, among the more important are polyethylene, polypropylene, polybutenes, polyisoprene and their copolymers. Many are produced in the form of fibers. This group comprises the largest tonnage of all thermoplastics produced.

polyorganosilicate graft polymer. An organoclay to which a monomer or an active polymer has been chemically bonded, often by the use of ionizing radiation. An example is the bonding of styrene to a polysilicate containing vinyl radicals, resulting in the growth of polystyrene chains from the surface of the silicate. Such complexes are stable to organic solvents. They have consid-